



THE UNIVERSITY *of* EDINBURGH

## Edinburgh Research Explorer

### Reduction of environmental pollutants for prevention of cardiovascular disease: it's time to act

**Citation for published version:**

Münzel, T, Miller, MR, Sorensen, M, Lelieveld, J, Daiber, A & Rajagopalan, S 2020, 'Reduction of environmental pollutants for prevention of cardiovascular disease: it's time to act', *European Heart Journal*.  
<https://doi.org/10.1093/eurheartj/ehaa745>

**Digital Object Identifier (DOI):**

[10.1093/eurheartj/ehaa745](https://doi.org/10.1093/eurheartj/ehaa745)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Publisher's PDF, also known as Version of record

**Published In:**

European Heart Journal

**General rights**

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy**

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



# Reduction of environmental pollutants for prevention of cardiovascular disease: it's time to act

Thomas Münzel <sup>1\*</sup>, Mark R. Miller <sup>2</sup>, Mette Sørensen <sup>3,4</sup>, Jos Lelieveld <sup>5</sup>,  
Andreas Daiber <sup>1†</sup>, and Sanjay Rajagopalan <sup>6\*†</sup>

<sup>1</sup>Department of Cardiology, University Medical Center Mainz, Johannes Gutenberg University, Langenbeckstrasse 1, 55131 Mainz, Germany; <sup>2</sup>University/BHF Centre for Cardiovascular Sciences, University of Edinburgh, UK; <sup>3</sup>Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark; <sup>4</sup>Department of Natural Science and Environment, Roskilde University, Roskilde, Denmark; <sup>5</sup>Max Planck Institute for Chemistry, Atmospheric Chemistry Department, Mainz, Germany; and <sup>6</sup>Division of Cardiovascular Medicine, Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, Case Western Reserve School of Medicine, 11100 Euclid Avenue, Cleveland, OH 44106, USA

Received 29 June 2020; revised 24 July 2020; editorial decision 22 August 2020; accepted 31 August 2020

## Introduction

Cardiovascular disease (CVD) represents the result of underlying genetic predisposition and lifetime exposure to multiple environmental factors. The past century has seen a revolution in our understanding of the importance of modifiable risk factors such as diet, exercise, and smoking. Exposure to environmental pollutants, be it in the air, water, or physical environment, is increasingly recognized as a silent, yet important determinant of CVD.<sup>1</sup> The quote 'genetics loads the gun but the environment pulls the trigger', put forward by G.A. Bray and F. Collins, exemplifies the complex relationship between human disease and the environment. The cardiovascular system is highly vulnerable to a variety of environmental insults, including tobacco smoke, solvents, pesticides, and other inhaled or ingested pollutants, as well as extremes in noise and temperature. While our understanding of multiple environmental factors continues to evolve, it is estimated that environmental air pollution and noise pollution alone may contribute to a substantial burden attributable to environmental factors as we currently understand them. It is important to note that noise and air pollution can have many of the same sources such as heavy industry, road and aircraft vehicles. In a recent in-depth report, the European Commission acknowledged that the societal costs for the combination noise and air pollution are nearly 1 trillion Euros, while the costs for alcohol and smoking are considerably less (50–120 and 540 billion Euro, respectively, see [https://ec.europa.eu/environment/integration/research/newsalert/pdf/air\\_noise\\_pollution\\_socioeconomic\\_status\\_links\\_IR13\\_en.pdf](https://ec.europa.eu/environment/integration/research/newsalert/pdf/air_noise_pollution_socioeconomic_status_links_IR13_en.pdf)).

The World Health Organization (WHO) calculates that 12.6 million premature deaths per year are attributable to unhealthy environments, 8.2 million of which are due to non-communicable disease, with CVD (including stroke) being the largest contributor, accounting for nearly 5 million of these deaths.<sup>2</sup> Among all environmental pollutants, poor air quality is the most important risk factor, and ambient air pollution due to particulate matter <2.5 µm (PM<sub>2.5</sub>) exposure ranks 5th among all global risk factors in 2015, leading to 4.2 million deaths annually as estimated by the Global Burden of Disease study.<sup>3</sup> Nine out of 10 people worldwide are exposed to ambient air pollutant levels above WHO guidelines (>10 µg/m).<sup>3,4</sup> Using a novel exposure-response hazard function (global estimate of exposure mortality model) to estimate global mortality attributable to air pollution, Burnett *et al.*<sup>5</sup> and Lelieveld *et al.*<sup>6</sup> found that around 9 million global premature deaths (790 000 excess deaths in Europe alone) were attributable to air pollution,<sup>7</sup> numbers that are well comparable to that of smoking.<sup>6</sup> These figures are substantially higher than those estimated by the WHO and Global Burden of Disease study.<sup>2,3</sup>

Ambient noise is the other omnipresent exposure with emerging data suggesting a large attributable burden of disability to this factor in many urban environments. In Western Europe, it is estimated that around 1.6 million healthy life years are lost every year due to noise. It is estimated that a large part of the European population is exposed to noise originating from road traffic at levels exceeding 55 decibels [dB(A), A-weighted decibel scale adapted to the human hearing frequencies]; 20% exposed to levels exceeding 65 dB(A) during the daytime; and 30% of the population is exposed to levels exceeding 55 dB(A) (see <https://www.eea.europa.eu/publications/environmen>).

\* Corresponding authors. Tel: +49 6131 17 7250, Fax: +49 6131 17 6615, Email: [tmuenzel@uni-mainz.de](mailto:tmuenzel@uni-mainz.de) (T.M.); Tel: +1 216-844-5125, Email: [sxr647@case.edu](mailto:sxr647@case.edu) (S.R.)

† These authors contributed equally to this study.

© The Author(s) 2020. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

tal-noise-in-europe). In this review, we will focus on the cardiovascular effects of ambient air pollution and noise pollution as prototypical environmental factors that provide important lessons to facilitate understanding of the outside effects of the environment on susceptibility to CVD. The pathophysiology, epidemiology, mitigation measures, and future challenges for these two common yet pervasive environmental factors are discussed in detail.

In many parts of the world, a substantial portion of the urban population is exposed to road traffic noise at levels exceeding 55 dB(A).<sup>8</sup> In cities in Asia, the proportion of the population reaching  $L_{den}$  levels (day–evening–night level, i.e. the average sound pressure level measured over a 24 h period with adjustment for more detrimental health effects of nocturnal noise) of 60–64 dB is very high.<sup>9</sup> In contrast to the relatively straightforward classification of noise, air pollution is intrinsically complex and defies easy classification. From a regulatory perspective, ‘criteria’ air pollutants allow health-based and/or environmentally based guidelines for setting permissible levels.<sup>10</sup> These include carbon monoxide, lead, nitrogen oxides, ground-level ozone, particle pollution (often referred to as PM), and sulphur oxides. Particulate matter is categorized based on its aerodynamic diameter:  $\leq 10 \mu\text{m}$  [thoracic particles ( $\text{PM}_{10}$ )],  $\leq 2.5 \mu\text{m}$  [fine particles ( $\text{PM}_{2.5}$ )],  $\leq 0.1 \mu\text{m}$  [ultrafine particles (UFP)], and between 2.5 and  $10 \mu\text{m}$  [coarse particles ( $\text{PM}_{2.5-10}$ )]. Although ‘criteria’ pollutants are regulated individually, it is anticipated that the effects of air pollution are driven by the complex interaction of particulate and gaseous components in mixtures and that smaller particles (e.g. UFP) are more detrimental than larger ones.

There is substantial spatial and temporal variation of both noise and air pollution. Traffic-related pollutants and noise often peak during the late morning and evening rush hours. Gradients for both noise and air pollutants are also dependent upon meteorological conditions, including diurnal changes in vertical mixing height, wind speed, and temperature. In the case of noise, the gradients are substantial as the intensity of noise decreases exponentially with the distance from its source. The gradients for air pollution from their source may also differ depending upon the pollutant. Traffic factors, such as the speed, traffic load, etc., may also differentially affect noise and traffic-related air pollution. During traffic congestion, when traffic is at standstill or at lower engine speeds, noise levels may be lower, but emissions may be dramatically higher, contributing to marked surges in traffic-related air pollutants. In contrast, when traffic is moving well, noise levels may be higher, but emissions may be lower. Environmental factors such as road conditions, noise barriers, and surrounding buildings are well known to influence traffic noise but may not influence air pollution substantially.

The highly associated nature of traffic noise and air pollution makes it challenging to isolate their independent effects on cardiovascular events in epidemiological studies. A few studies have attempted to assess the independent contribution of noise from air pollution and vice versa. The results are, however, somewhat variable, with some studies demonstrating an independent effect of noise and/or air pollution on cardiovascular morbidity and mortality, while others find marked attenuation of effects after adjusting for the other. Whether noise and air pollution have differing, additive, synergistic, and/or confounding effects upon cardiovascular health is still incompletely understood. Also of great importance in all air pollution and noise exposure studies is the co-linearity of these

risk factors to other confounders (e.g. lower socio-economic status, psychosocial stressors, other poorly understood environmental variables and adverse lifestyle factors) that often go hand-in-hand with pollutants.

## Pathophysiology and epidemiology of noise and cardiovascular disease

### Epidemiology

During the last decade, a number of epidemiological studies have investigated effects of transportation noise on risk for CVD. In 2018, a systematic review by WHO found that there was substantial evidence to conclude that road traffic noise increases the risk for ischaemic heart disease, with an 8% higher risk per 10 dB higher noise.<sup>11</sup> For stroke, the evidence was ranked as moderate, with only one study on incidence and four on mortality.<sup>11</sup> Subsequently, large population-based studies from Frankfurt, London, and Switzerland found road traffic noise to increase stroke incidence and/or mortality, especially ischaemic strokes,<sup>12–14</sup> whereas smaller cohort studies indicated no association.<sup>15</sup> Recently, road traffic noise has been found to increase the risk for other major CVD not evaluated by WHO, most importantly heart failure and atrial fibrillation.<sup>14,16</sup> Aircraft noise has also been associated with higher CVD incidence and mortality,<sup>14,17</sup> but due to a limited number of studies, the evidence is still rated low to moderate.<sup>18</sup>

Epidemiological studies have linked transportation noise with a number of major cardiovascular risk factors, most consistently obesity and diabetes.<sup>19,20</sup> Also, many studies investigated effects of noise on hypertension, and although a meta-analysis of 26 studies found that road traffic noise was associated with higher prevalence of hypertension,<sup>11</sup> studies on incidence are still few and inconsistent.

Ambient air pollution and traffic noise, especially from roads, are correlated and suspected of being associated with the same CVD, and therefore mutual adjustment is highly important. Most recent studies on noise and CVD adjust for air pollution and generally the results are found to be robust to the adjustment, suggesting that transportation noise is indeed an independent risk factor for CVD.<sup>21</sup>

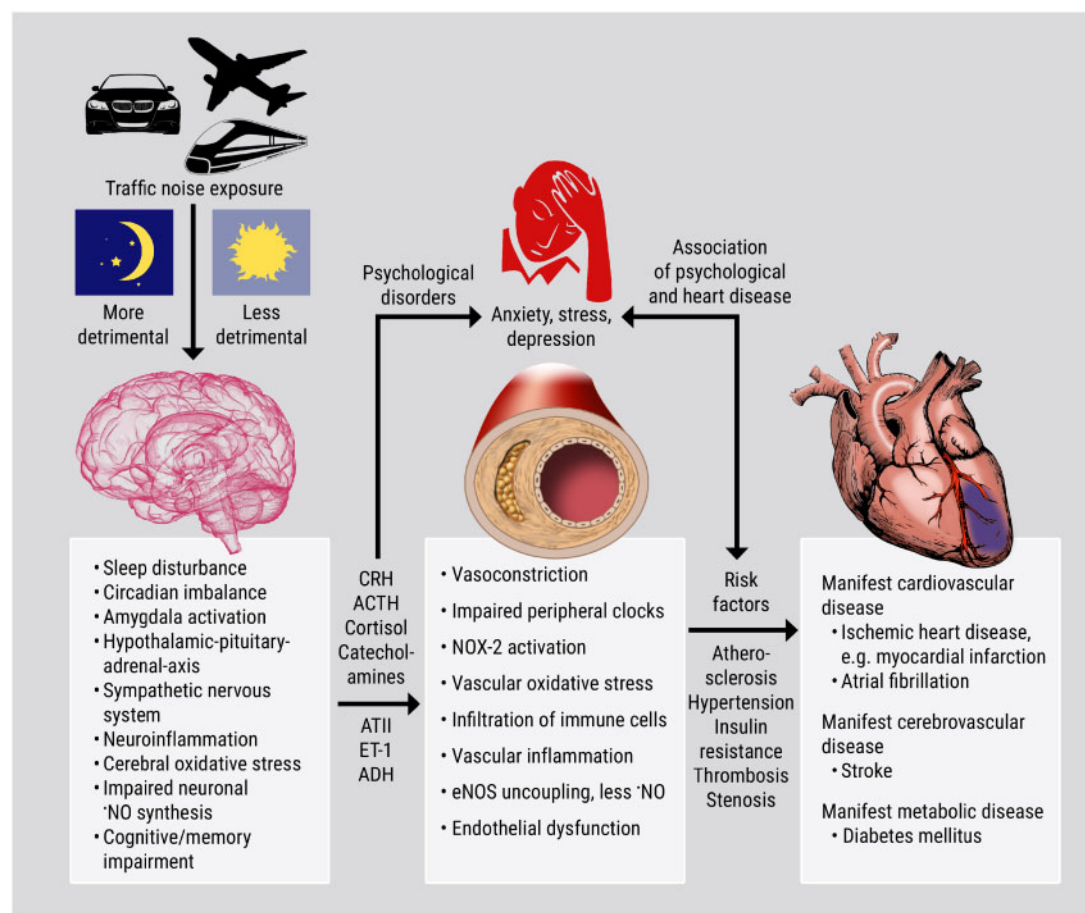
Another noise source investigated in relation to CVD risk is occupational noise; an exposure mainly occurring during daytime. Most existing studies are cross-sectional, and results from a few prospective studies providing conflicting evidence, with some studies indicating an association with CVD,<sup>22</sup> whereas others finding no association,<sup>23</sup> stressing the need for more well-designed prospective studies.

### Pathophysiology

According to the noise stress reaction model introduced by Babisch,<sup>24</sup> non-auditory health effects of noise have been demonstrated to activate a so-called ‘indirect pathway’, which in turn represents the cognitive perception of the sound, and its subsequent cortical activation is related to emotional responses such as annoyance and anger (reviewed in Ref. 25). This stress reaction chain can initiate physiological stress responses, involving the hypothalamus, the limbic system, and the autonomic nervous system with activation

of the hypothalamus–pituitary–adrenal (HPA) axis and the sympathetic–adrenal–medulla axis, and is associated with an increase in heart rate and in levels of stress hormones (cortisol, adrenalin, and noradrenaline) enhanced platelet reactivity, vascular inflammation, and oxidative stress (see Figure 1). While the conscious experience with noise might be the primary source of stress reactions during daytime (for transportation and occupational noise), the sub-conscious biological response during night-time in sleeping subjects, at much lower transportation noise levels, is thought to play an important role in pathophysiology, particularly through disruption of sleep–wake cycle, diurnal variation, and perturbation of time periods critical for physiological and mental restoration. Recent human data provided a molecular proof of the important pathophysiological role of this ‘indirect pathway’ by identifying amygdalar activation (using  $^{18}\text{F}$ -FDGPET/CT imaging) by transportation noise in 498 subjects, and its association with arterial inflammation and major adverse

cardiovascular events.<sup>27</sup> These data are indeed consistent with animal experiments demonstrating an increased release of stress hormones (catecholamines and cortisol), higher blood pressure, endothelial dysfunction,<sup>28</sup> neuroinflammation, diminished neuronal nitric oxide synthase (nNOS) expression as well as cerebral oxidative stress in aircraft noise-exposed mice.<sup>29</sup> These changes were substantially more pronounced when noise exposure was applied during the sleep phase (reflecting night-time noise exposure) and was mostly prevented in mice with genetic deletion or pharmacological inhibition of the phagocytic NADPH oxidase (NOX-2).<sup>29</sup> These studies also revealed substantial changes in the gene regulatory network by noise exposure, especially within inflammatory, antioxidant defence, and circadian clock pathways (Figure 1).<sup>28,29</sup> The conclusions from these experiments are supportive of a role for shortened sleep duration and sleep fragmentation in cerebrovascular oxidative stress and endothelial dysfunction.



**Figure 1** The key mechanisms of the adverse health effects of traffic noise exposure. Environmental noise exposure causes mental stress responses, a neuroinflammatory phenotype, and cognitive decline. This may lead to manifest psychological disorders and mental diseases or, via stress hormone release and induction of potent vasoconstrictors, to vascular dysfunction and damage. All of these mechanisms initiate cardio-metabolic risk factors that lead to manifest end organ damage. Of note, chronic cardio-metabolic diseases often are associated with psychological diseases and vice versa.<sup>26</sup> • ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone (vasopressin); ATII, angiotensin II; CRH, corticotropin-releasing hormone; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; NO, nitric oxide; NOX-2, phagocytic NADPH oxidase (catalytic subunit).

Likewise, we observed a significant degree of endothelial dysfunction, an increase in stress hormone release, blood pressure and a decrease in sleep quality in healthy subjects and patients with established coronary artery disease, in response to night-time aircraft noise (reviewed in Ref.<sup>25</sup>). Importantly, endothelial dysfunction was corrected by the antioxidant vitamin C indicating increased vascular oxidative stress in response to night-time aircraft noise exposure. The important role of oxidative stress and inflammation for noise-induced cardiovascular complications was also supported by changes of the plasma proteome, centred on redox, pro-thrombotic and proinflammatory pathways, in subjects exposed to train noise for one night [mean SPL 54 dB(A)].<sup>30</sup>

## Pathophysiology and epidemiology of air pollution and cardiovascular disease

Since the publication of an American Heart Association Scientific Statement,<sup>31</sup> there has been a consistent stream of epidemiological and mechanistic evidence linking PM<sub>2.5</sub>, the most frequently implicated air pollution component with CVD.<sup>5,6</sup> Mounting evidence suggests that health risks attributable to PM<sub>2.5</sub> persist even at low levels, below WHO air quality guidelines and European standards (annual levels <10 and <25 µg/m<sup>3</sup>, respectively). Updated exposure-response dose curves suggest a robust supralinear concentration-response-curve for PM and CVD with no apparent safe threshold level.<sup>32</sup>

### Epidemiology

Current estimates suggest air pollution is associated with around 9 million premature deaths, worldwide annually with ~40–60% of mortality attributed to cardiovascular causes.<sup>5,33</sup> Short-term exposure (over hours or days) is associated with increased risk for myocardial infarction, stroke, heart failure, arrhythmia, and sudden death by about 1–2% per 10 µg/m<sup>3</sup>. Longer-term exposure over months or years, amplifies these risk associations, to 5–10% per 10 µg/m<sup>3</sup>. Living in regions with poor air quality potentiates the atherosclerotic process and promotes the development of several chronic cardiometabolic conditions (e.g. diabetes, hypertension).

Although the strength of the association for criteria air pollutants is strongest for PM<sub>2.5</sub>, there are data linking other pollutants such as nitrogen oxides (e.g. NO<sub>2</sub>) and less consistently ozone (O<sub>3</sub>) with cardiovascular events.<sup>32</sup> Pollutants from traffic and combustion sources are of high concern (due to high levels of ultrafine PM, toxicity of constituents, and penetration of pollutants systemically) although precise burden estimates have yet to be established for this source. Coarse PM<sub>10</sub> air pollution from anthropogenic sources has been associated with cardiovascular disease although sources such as agricultural emissions and crustal material are less well studied.

Given the continuing links between PM<sub>2.5</sub> and adverse cardiovascular events, even at levels substantially below 10 µg/m<sup>3</sup>, there is a need for a realistic lower limit that may strike the balance between what is reasonably possible and eliminating anthropogenic sources. It is important to keep in mind that complete elimination of all PM<sub>2.5</sub>

may not be possible given that some PM<sub>2.5</sub> is natural. Calculations by Lelieveld et al.<sup>33</sup> of a complete phase-out of fossil fuel-related emissions (needed to achieve the 2°C climate change goal under the Paris Agreement) demonstrated a reduction in excess mortality rate of 3.61 million per year worldwide. The increase in mean life expectancy in Europe would be around 1.2 years indicating a tremendous health co-benefit from the phase-out of carbon dioxide emissions.

### Pathophysiology

Mechanistic studies, using controlled exposure studies in humans and experimental models support a causal relationship between PM and CVD. Acute exposure to air pollutants induces rapid changes that include vasoconstriction, endothelial dysfunction, arterial stiffening, arrhythmia, exacerbation of cardiac ischaemia, increased blood coagulability, and decreased fibrinolytic capacity. Additionally, long-term exposure to PM accelerates the growth and vulnerability of atherosclerotic plaques.<sup>34</sup> A broad range of mechanisms accounts for pathophysiology at an organ and cellular level, with inflammation and oxidative stress playing key roles.<sup>25</sup> Additionally, several convincing pathways can account for the link between inhalation of pollutants and the cardiovascular system, including passage of inflammatory (and other) mediators into the circulation, direct passage of particles (or their constituents) into circulation, imbalance of autonomic nervous system activity, and changes to central control of endocrine systems. The contribution of individual pathways will depend on type of pollutant, the exposure (dose and duration), specific cardiovascular endpoints, and the health status of individual. Finally, the cardiovascular effects of pollutants occur in both healthy individuals and those with pre-existing cardiorespiratory disease, suggesting a potential contributory role on the induction, progression, and exacerbation of CVD.<sup>32,34</sup>

## Mitigation strategies

### Noise mitigation

In 2020, the European Environment Agency concluded that more than 20% of the EU population live with road traffic noise levels that are harmful to health and that this proportion is likely to increase in the future (see <https://www.eea.europa.eu/publications/environmental-noise-in-europe> [last accessed 17/09/2020]). European Environment Agency also estimated that in EU, 22 million live with high railway noise and 4 million with high aircraft noise.

The authorities can use different strategies to reduce levels of traffic noise (Table 1). For road traffic, the sound generated by the contact between the tires and the pavement is the dominant noise source, at speeds above 35 km/h for cars and above 60 km/h for trucks. Therefore, changing to electric cars will result in only minor reductions in road traffic noise. Generally applied strategies for reducing road traffic noise include noise barriers in densely populated areas, applying quiet road surfaces, and reducing speed, especially during night-time. Furthermore, there is a great potential in developing and using low-noise tires. As many of these mitigation methods result in only relatively small changes in noise (Table 1), a combination of different methods is important in highly exposed areas. For aircraft noise, mitigation strategies include to minimizing overlapping of air



**Table 1** Mitigation methods resulting in reduction in road traffic noise

Change in noise	Perceived change	Methods for noise reduction
1 dB	A very small change.	Reduce speed by 10 km/h Replace all cars with electric cars Shift traffic from night-time to day-time period Remove 25% of the traffic
3 dB	An audible, but small change.	Reduce speed by 30 km/h Apply quiet road surfaces Use low-noise emitting tires Remove 50% of the traffic
5 dB	A substantial change.	Build noise barriers Remove 65% of traffic
10 dB	A large change. Sounds like a halving of the sound.	Build high noise barriers Remove 90% of the traffic Sound-reducing windows

traffic routes and housing zones, introduction of night bans, and implementation of continuous descent arrivals, which require the aircraft to approach on steeper descents with lower, less variable throttle settings. For railway noise, replacing cast-iron block breaks with composite material, grinding of railway tracks and night bans, are among the preferred strategies for reducing noise. Lastly, installing sound-reducing windows and/or orientation of the bedroom towards the quiet side of the residence can reduce noise exposure.

## Air pollution mitigation

Although it is widely recognized that legislation, policies, regulation, and technology, coupled with enforcement, are critical to reduction of air pollution levels, the political momentum required to accomplish this globally is currently limited. Thus, personal measures to mitigate risk take on a much greater importance. The current experience and lessons learned with personal protective equipment and mitigation in reducing exposure to SARS-CoV2 are highly reminiscent of their use in combating air pollution, albeit the protection provided varies depending on the pollutant.<sup>35</sup> Mitigation measures must be affordable and broadly applicable to the population, and the level of protection provided should match the risk of population that is being exposed (Figure 2). The latter would necessitate an understanding of the health risk of the patient/community and degree of exposure. The need and urgency plus intensity of any recommended intervention also need to be weighed against their potential benefits vs. risks for each individual (e.g. wasted effort, resources, unnecessary concern, or possible complacency of the user). Although no intervention to reduce air pollution exposure has as yet been shown to reduce cardiovascular events, the consistent link between increased levels of PM<sub>2.5</sub> and cardiovascular events, evidence for measures in lowering PM<sub>2.5</sub> levels, and the impact of several mitigation strategies in improving surrogate markers are highly suggestive that interventions could be correspondingly impactful in reducing cardiovascular events.

Current approaches to mitigate air pollution and their impact have been previously reviewed and can be broadly classified into: (i) Active

personal exposure mitigation with home air cleaning and personal equipment (Table 2); (ii) Modification of human behaviour to reduce passive exposures; (iii) Pharmacologic approaches.<sup>32</sup> Studies on N95 respirator under ambient PM<sub>2.5</sub> exposure conditions at both high and low levels of exposures over a few hours have shown to reduce systolic blood pressure and improve heart rate variability.<sup>32,36</sup> In the only trial comparing exposure mitigation to both noise and air pollution, individual reduction of air pollution or noise with a respirator or noise-cancelling headphones, respectively, did not alter blood pressure. Heart rate variability indices were, however, variably improved with either intervention.<sup>37</sup> Face masks and procedural masks (e.g. surgical masks) are widely available but are not effective in filtering PM<sub>2.5</sub>, especially if poorly fitting or worn during high activity,<sup>38</sup> and therefore cannot be recommended for widespread usage if N95 respirators are available. Closing car windows, air-conditioning, and cabin air filters represent approaches that could be important in those who are susceptible, but only in those spending large amounts of time in transportation microenvironments. Behavioural strategies such as air pollution avoidance by changing travel routes, staying indoors/closing windows, and modification of activity can help limit air pollution exposure, but unintended consequences in some instances have the potential of offsetting benefit. An example is closing windows to limit outdoor exposure but increasing the hazard for indoor air pollutants or limiting outdoor recreation/exercise to mitigate ambient exposures. The latter scenario of limiting outdoor exposure brings up some very practical questions about the risk/benefit of loss of cardiovascular benefits of exercise vs. potential gain from benefits secondary to air pollution mitigation. Health impact modelling and epidemiologic studies have demonstrated that the benefits of aerobic exercise nearly always exceed the risk of air pollution exposure across a range of concentrations, and for long durations of exercise for normal individuals (>75 min). Based on current evidence, guiding healthy people to avoid outdoor activity in areas with high PM<sub>2.5</sub> pollution has the potential to produce greater harm than benefit, given the low absolute risk for cardiovascular or respiratory events. On the other hand, advising patients with pre-established CVD to continue



**Figure 2** Mitigation measures to reduce air pollution exposure.

to remain >400 m away from major roadways to avoid exposure to traffic pollutants is a reasonable measure, despite the current lack of strong evidentiary support.

Although a variety of over the counter drugs and medications have been shown to mitigate association between air pollution and surrogates, almost none can be recommended to protect against air pollution mediated adverse health effects at this time. However, the use of medications for primary and secondary prevention of CHD should be encouraged if indicated for other reasons.

## Housing and urban design to improve cardiovascular health

Two-third of the European population live in urban areas and this number continues to grow. A recent Statement on Air Quality Policy has discussed aspects in the built environment that may be targeted in order to reduce exposures to PM<sub>2.5</sub> (in press 2020). Briefly, built environment features may directly or indirectly modify adverse cardiovascular effects of air pollution through the indoor living environment, green spaces, roads, utilities, and transportation infrastructure. The design of communities has the potential of impacting exposures, by affecting the continuum of human existence across indoor living,

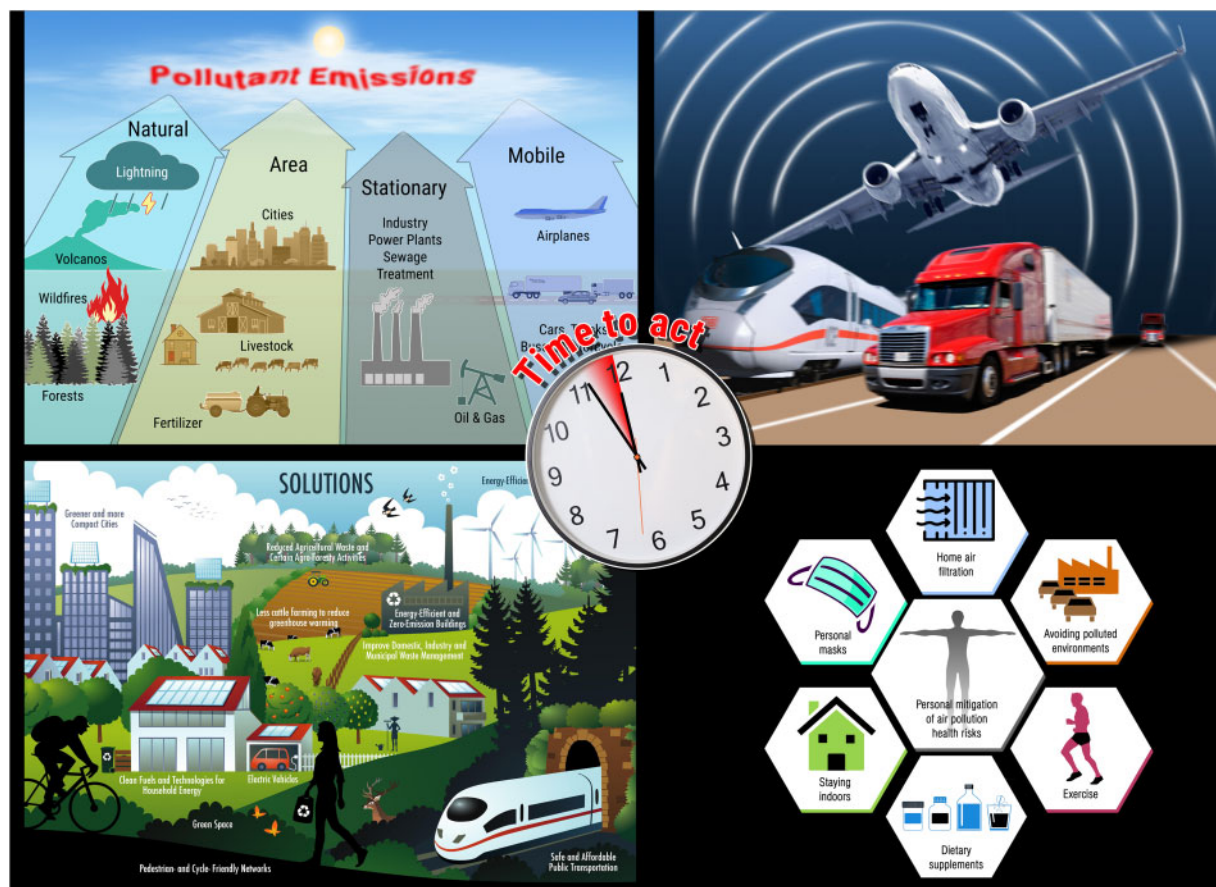
commuting, working, and recreation (Figure 3). The layout of roads, sidewalks, green spaces, and the availability of cheap public transportation can affect travel behaviour and can help alleviate air quality.<sup>39</sup> Communities with proximity and compactness have been associated with higher life expectancy, improved air quality, and health.<sup>40,41</sup> Green environments can improve air quality, encourage physical activity, and promote social interactions, ultimately improving cardiovascular health. Indeed, there is evidence to support a protective association of green spaces on PM-associated CVD.<sup>42,43</sup> All-cause and ischaemic heart disease mortality related to income deprivation has been shown to be lower in populations who live in the greenest areas, vs. those who have less exposure to green space.<sup>44</sup> Recently, Giles-Corti identified eight integrated regional and local interventions that, when combined, encourage walking, cycling and public transport use, while reducing private motor vehicle use.<sup>45</sup> These eight interventions are directed to reduce traffic exposure, to reduce air pollution and noise, and to reduce the important public health issue loneliness and social isolation, to improve the safety from crime, to reduce physical inactivity and prolonged sitting, and to prevent the consumption of unhealthy diets.<sup>45</sup>

**Table 2** Personal active mitigation methods to reduce air pollution exposure

Type of intervention	Efficacy in reducing exposure	Considerations for use	Evidence in reducing surrogate outcomes
Personal air purifying respirators (reducing solid but not gaseous air pollutants).			
N95 respirators	Highly effective in reducing PM <sub>2.5</sub> . Removes >95% inhaled particles at 0.3 µm in size	Fit and use frequency are key determinants of efficacy. A valve or microventilator fan may reduce humidity and enhance comfort. Uncomfortable to wear over long periods	Randomized controlled clinical trials over short durations (typically up to 48 h) with evidence for reducing blood pressure and improving heart rate variability indices.
Surgical and cloth masks	Not uniformly effective in reducing PM <sub>2.5</sub> exposure	While few studies suggest that these may reduce exposure, highly variable in efficacy.	Not recommended owing to variability in reducing exposure to particles
Portable air cleaners (PAC)			
Portable devices with high efficiency-particulate airfilter (HEPA) Filters. Electrostatic PACs additionally ionize particles	Designed to clean air in a small area. Effective in reducing indoor particles but duration of use and volume of room, key determinants of efficacy.	Efficacy related to clean air delivery rate normalized by room volume, which must be competitive with ventilation and deposition (loss) rates. Electrostatic PACs may result in ozone production	Overall trend in studies suggest a benefit on blood pressure and heart rate variability
Heating ventilation and air-conditioning (HVAC)			
Installed centrally in homes with filters that reduce exposure.	Effective in reducing concentrations as long as filters replaced regularly.	Efficacy is variable with building and operational factors (i.e. open windows)	No data currently available

**Figure 3** Urban design considerations to reduce exposure to noise and air pollution.





Upper left panel reused from Münzel T, Steven S, Frisic K, Lelieveld J, Hahad O, Dalber A. Environmental Factors Such as Noise and Air Pollution and Vascular Disease. Antioxid. Redox Signal. 2020;33:581-601. With permission by Mary Ann Liebert Inc.

**Take home figure** Upper left panel reproduced from Münzel et al.<sup>46</sup> with permission.

## Future perspectives: opportunities and challenges over the next decade

Efforts to mitigate air pollution and noise are endeavours that involve complex economic and geopolitical considerations. Measures such as transportation reform, shift to zero-emission fuels, urban landscape reform, and ecologically sound lifestyle changes may help simultaneously alleviate air/noise pollution while accomplishing climate change goals. However, reducing air pollution and noise may have short-term challenges due to economic incentives that are substantially misaligned with health and environmental priorities and thus opportunities to understand the importance of these factors in human health will sadly continue. An important avenue of investigation is convergent studies that look at the broad and collective impact and burden of air and noise pollution as archetypal environmental risk factors. The questions that need to be addressed are many and include the magnitude and time course of response of co-exposure, interactive effects of environmental factors on surrogate measures, duration of effect/time course of reversal, impact on circadian rhythm, and finally the effect of reversal as well as prevention and lifestyle approaches that may help mitigate risk (e.g. diet, stress, and exercise).

The rapid development of personalized technologies that provide multiple measures of health in fine temporal detail in conjunction with data on environmental exposure provide an unprecedented opportunity for research and may allow an extraordinary understanding of the interactions between environmental and non-environmental risk factors over long durations. Together with developments in next-generation sequencing technologies, and opportunities in big data, assimilative studies of this nature may finally provide a granular view of the environmental-genetic interactions leading to the development of CVD. However, the extent of these advances may be tempered by the need to manage subject burden and costs, and imprecise data on many environmental variables. Increased awareness of the societal burden posed by environmental risk factors and acknowledgement in traditional risk factor guidelines may pressurize politicians to intensify the efforts required for effective legislation.

The cardiovascular community has a responsibility to help promulgate the impact of, not only health lifestyle and diet, but also over the outsize impact of air and noise pollution on cardiovascular health. Individuals can apply political pressure through democratic means

and lobbying to enact changes at regional and national levels that lead to reductions in noise/air pollution exposure. Patient organization can provide a strong voice in the call for action at governmental level. Importantly, air pollution was mentioned in the published guidelines for cardiovascular prevention, but the recommendations to reduce pollution were completely insufficient,<sup>47</sup> while prevention measures with respect to traffic noise were completely lacking. Noise and air pollution represent significant cardiovascular risk factors, it is important that these factors are included into the ESC guidelines, and others, for myocardial infarction, arterial hypertension, and heart failure.

## Acknowledgements

We are indebted to the expert graphical assistance of Margot Neuser.

## Funding

A.D. and T.M. were supported by vascular biology research grants from the Boehringer Ingelheim Foundation for the collaborative research group 'Novel and neglected cardiovascular risk factors: molecular mechanisms and therapeutics' with continuous research support from Foundation Heart of Mainz. T.M. is PI of the DZHK (German Center for Cardiovascular Research), Partner Site Rhine-Main, Mainz, Germany. M.R.M. is supported by the British Heart Foundation (CH/09/002). S.R. was supported in part by the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH) under Award Numbers U01ES026721 and 5R01ES019616-07 and 1R01ES026291.

**Conflict of interest:** none declared.

## References

- Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, Balde AB, Bertollini R, Bose-O'Reilly S, Boufford JL, Breyse PN, Chiles T, Mahidol C, Coll-Seck AM, Cropper ML, Fobil J, Fuster V, Greenstone M, Haines A, Hanrahan D, Hunter D, Khare M, Krupnick A, Lanphear B, Lohani B, Martin K, Mathiasen KV, McTeer MA, Murray CJL, Ndahimananjara JD, Perera F, Potocnik J, Preker AS, Ramesh J, Rockstrom J, Salinas C, Samson LD, Sandilya K, Sly PD, Smith KR, Steiner A, Stewart RB, Suk WA, van Schayck OCP, Yadama GN, Yumkella K, Zhong M. The Lancet Commission on pollution and health. *Lancet* 2018;**391**: 462–512.
- Aronow WS. Drug treatment of elderly patients with acute myocardial infarction: practical recommendations. *Drugs Aging* 2001;**18**:807–818.
- Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, Balakrishnan K, Brunekreef B, Dandona L, Dandona R, Feigin V, Freedman G, Hubbell B, Jobling A, Kan H, Knibbs L, Liu Y, Martin R, Morawska L, Pope CA 3rd, Shin H, Straif K, Shaddick G, Thomas M, van Dingenen R, van Donkelaar A, Vos T, Murray CJL, Forouzanfar MH. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017;**389**:1907–1918.
- Hirose R, Okumura H, Yoshimatsu A, Irie J, Onoda Y, Nomoto Y, Takai H, Ohno T, Ichimura M. KF31327, a new potent and selective inhibitor of cyclic nucleotide phosphodiesterase 5. *Eur J Pharmacol* 2001;**431**:17–24.
- Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA 3rd, Apte JS, Brauer M, Cohen A, Weichenthal S, Coggins J, Di Q, Brunekreef B, Frostad J, Lim SS, Kan H, Walker KD, Thurston GD, Hayes RB, Lim CC, Turner MC, Jerrett M, Krewski D, Gapstur SM, Diver WR, Ostro B, Goldberg D, Crouse DL, Martin RV, Peters P, Pinault L, Tjepkema M, van Donkelaar A, Villeneuve PJ, Miller AB, Yin P, Zhou M, Wang L, Janssen NAH, Marra M, Atkinson RW, Tsang H, Quoc Thach T, Cannon JB, Allen RT, Hart JE, Laden F, Cesaroni G, Forastiere F, Weinmayr G, Jaensch A, Nagel G, Concin H, Spadaro JV. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci U S A* 2018;**115**:9592–9597.
- Lelieveld J, Pozzer A, Poschl U, Fnaiss M, Haines A, Munzel T. Loss of life expectancy from air pollution compared to other risk factors: a worldwide perspective. *Cardiovasc Res* 2020;**116**:1910–1917.
- Lelieveld J, Munzel T. Air pollution, chronic smoking, and mortality. *Eur Heart J* 2019;**40**:3204.
- Kalsch H, Hennig F, Moebus S, Mohlenkamp S, Dragano N, Jakobs H, Memmesheimer M, Erbel R, Jockel K-H, Hoffmann B, Roggenbuck U, Slomiany U, Beck EM, Offner A, Munkel S, Schrader S, Peter R, Hirche H, Meinertz T, Bode C, deFeyer PJ, Guntert B, Halli T, Gutzwiller F, Heinen H, Hess O, Klein B, Lowel H, Reiser M, Schmidt G, Schwaiger M, Steinmuller C, Theorell T, Willich SN; on behalf of the Heinz Nixdorf Recall Study Investigative Group. Are air pollution and traffic noise independently associated with atherosclerosis: the Heinz Nixdorf Recall Study. *Eur Heart J* 2014;**35**:853–860.
- Brown AL, Lam KC, van Kamp I. Quantification of the exposure and effects of road traffic noise in a dense Asian city: a comparison with western cities. *Environ Health* 2015;**14**:22.
- EPA US. *Air Quality Criteria for Particulate Matter*; December 2016. <https://www.epa.gov/criteria-air-pollutants/naaqs-table>
- Kempen EV, Casas M, Pershagen G, Foraster M. WHO environmental noise guidelines for the European region: a systematic review on environmental noise and cardiovascular and metabolic effects: a summary. *Int J Environ Res Public Health* 2018;**15**:379.
- Seidler AL, Hegewald J, Schubert M, Weihofen VM, Wagner M, Droge P, Swart E, Zeeb H, Seidler A. The effect of aircraft, road, and railway traffic noise on stroke—results of a case-control study based on secondary data. *Noise Health* 2018;**20**:152–161.
- Halonen JJ, Hansell AL, Gulliver J, Morley D, Blangiardo M, Fecht D, Toledano MB, Beevers SD, Anderson HR, Kelly FJ, Tonne C. Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London. *Eur Heart J* 2015;**36**:2653–2661.
- Héritier H, Vienneau D, Foraster M, Eze IC, Schaffner E, Thiesse L, Rudzik F, Habermacher M, Köpfli M, Pieren R, Brink M, Cajochen C, Wunderli JM, Probst-Hensch N, Röösli M; SNC Study Group. Transportation noise exposure and cardiovascular mortality: a nationwide cohort study from Switzerland. *Eur J Epidemiol* 2017;**32**:307–315.
- Cai Y, Hodgson S, Blangiardo M, Gulliver J, Morley D, Fecht D, Vienneau D, de Hoogh K, Key T, Hveem K, Elliott P, Hansell AL. Road traffic noise, air pollution and incident cardiovascular disease: a joint analysis of the HUNT, EPIC-Oxford and UK Biobank cohorts. *Environ Int* 2018;**114**:191–201.
- Monrad M, Sajadieh A, Christensen JS, Ketzel M, Raaschou-Nielsen O, Tjønneland A, Overvad K, Loft S, Sørensen M. Residential exposure to traffic noise and risk of incident atrial fibrillation: a cohort study. *Environ Int* 2016;**92–93**:457–463.
- Hansell AL, Blangiardo M, Fortunato L, Floud S, de HK, Fecht D, Ghosh RE, Laszlo HE, Pearson C, Beale L, Beevers S, Gulliver J, Best N, Richardson S, Elliott P. Aircraft noise and cardiovascular disease near Heathrow airport in London: small area study. *BMJ* 2013;**347**:f5432.
- Kempen EV, Casas M, Pershagen G, Foraster M. WHO environmental noise guidelines for the European region: a systematic review on environmental noise and cardiovascular and metabolic effects: a summary. *Int J Environ Res Public Health* 2018;**15**:379.
- Zare Sakhvidi MJ, Zare Sakhvidi F, Mehrparvar AH, Foraster M, Dadvand P. Association between noise exposure and diabetes: a systematic review and meta-analysis. *Environ Res* 2018;**166**:647–657.
- Pyko A, Eriksson C, Lind T, Mitkovskaya N, Wallas A, Ogren M, Ostenson CG, Pershagen G. Long-term exposure to transportation noise in relation to development of obesity—a cohort study. *Environ Health Perspect* 2017;**125**:117005.
- Thacher JD, Hvidtfeldt UA, Poulsen AH, Raaschou-Nielsen O, Ketzel M, Brandt J, Jensen SS, Overvad K, Tjønneland A, Münzel T, Sørensen M. Long-term residential road traffic noise and mortality in a Danish cohort. *Environ Res* 2020;**187**: 109633.
- Eriksson HP, Andersson E, Schioler L, Soderberg M, Sjöström M, Rosengren A, Toren K. Longitudinal study of occupational noise exposure and joint effects with job strain and risk for coronary heart disease and stroke in Swedish men. *BMJ Open* 2018;**8**:e019160.
- Stokholm ZA, Bonde JP, Christensen KL, Hansen AM, Kolstad HA. Occupational noise exposure and the risk of stroke. *Stroke* 2013;**44**:3214–3216.
- Babisch W. The noise/stress concept, risk assessment and research needs. *Noise Health* 2002;**4**:1–11.
- Munzel T, Sorensen M, Gori T, Schmidt FP, Rao X, Brook FR, Chen LC, Brook RD, Rajagopalan S. Environmental stressors and cardio-metabolic disease: part II—mechanistic insights. *Eur Heart J* 2016;**38**:557–564.
- Hahad O, Prochaska JH, Daiber A, Münzel T. Environmental noise-induced effects on stress hormones, oxidative stress, and vascular dysfunction: key factors in the relationship between cerebrocardiovascular and psychological disorders. *Oxid Med Cell Longev* 2019;**2019**:1–13.
- Osborne MT, Radfar A, Hassan MZO, Abohashem S, Oberfeld B, Patrich T, Tung B, Wang Y, Ishai A, Scott JA, Shin LM, Fayad ZA, Koenen KC, Rajagopalan

- S, Pitman RK, Tawakol A. A neurobiological mechanism linking transportation noise to cardiovascular disease in humans. *Eur Heart J* 2020;**41**:772–782.
28. Münzel T, Daiber A, Steven S, Tran LP, Ullmann E, Kossmann S, Schmidt FP, Oelze M, Xia N, Li H, Pinto A, Wild P, Pies K, Schmidt ER, Rapp S, Kröller-Schön S. Effects of noise on vascular function, oxidative stress, and inflammation: mechanistic insight from studies in mice. *Eur Heart J* 2017;**38**:2838–2849.
29. Kröller-Schön S, Daiber A, Steven S, Oelze M, Frenis K, Kalinovic S, Heimann A, Schmidt FP, Pinto A, Kvandova M, Vujacic-Mirski K, Filippou K, Dudek M, Bosmann M, Klein M, Bopp T, Hahad O, Wild PS, Frauenknecht K, Methner A, Schmidt ER, Rapp S, Mollnau H, Münzel T. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. *Eur Heart J* 2018;**39**:3528–3539.
30. Herzog J, Schmidt FP, Hahad O, Mahmoudpour SH, Mangold AK, Garcia Andreo P, Prochaska J, Koeck T, Wild PS, Sørensen M, Daiber A, Münzel T. Acute exposure to nocturnal train noise induces endothelial dysfunction and prothrombotic inflammatory changes of the plasma proteome in healthy subjects. *Basic Res Cardiol* 2019;**114**:46.
31. Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC Jr, Whitsett L, Kaufman JD, American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation* 2010;**121**:2331–2378.
32. Al-Kindi S, Brook RD, Biswal S, Rajagopalan S. Environmental determinants of cardiovascular disease: lessons learned from air pollution. *Nat Rev Cardiol* 2020;**17**:656–672.
33. Lelieveld J, Klingmüller K, Pozzer A, Poschl U, Fnaiss M, Daiber A, Münzel T. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. *Eur Heart J* 2019;**40**:1590–1596.
34. Miller MR, Newby DE. Air pollution and cardiovascular disease: car sick. *Cardiovasc Res* 2020;**116**:279–294.
35. Rajagopalan S, Huang S, Brook RD. Flattening the curve in COVID-19 using personalised protective equipment: lessons from air pollution. *Heart* 2020;**106**:1286–1288.
36. Langrish JP, Li X, Wang S, Lee MM, Barnes GD, Miller MR, Cassee FR, Boon NA, Donaldson K, Li J, Li L, Mills NL, Newby DE, Jiang L. Reducing personal exposure to particulate air pollution improves cardiovascular health in patients with coronary heart disease. *Environ Health Perspect* 2012;**120**:367–372.
37. Yang X, Jia X, Dong W, Wu S, Miller MR, Hu D, Li H, Pan L, Deng F, Guo X. Cardiovascular benefits of reducing personal exposure to traffic-related noise and particulate air pollution: a randomized crossover study in the Beijing subway system. *Indoor Air* 2018;**28**:777–786.
38. Cherrie JW, Apsley A, Cowie H, Steinle S, Mueller W, Lin C, Horwell CJ, Sleeuwenhoek A, Loh M. Effectiveness of face masks used to protect Beijing residents against particulate air pollution. *Occup Environ Med* 2018;**75**:446–452.
39. United States Department of Environmental Protection. Our Built and Natural Environments: A Technical Review of the Interactions Among Land Use, Transportation, and Environmental Quality. 2013. U.S. Environmental Protection Agency, Washington, USA.
40. Hamidi S, Ewing R, Tatalovich Z, Grace JB, Berrigan D. Associations between Urban Sprawl and Life Expectancy in the United States. *Int J Environ Res Public Health* 2018;**15**:861.
41. Hankey S, Marshall JD. Urban form, air pollution, and health. *Curr Environ Health Rep* 2017;**4**:491–503.
42. Heo S, Bell ML. The influence of green space on the short-term effects of particulate matter on hospitalization in the U.S. for 2000–2013. *Environ Res* 2019;**174**:61–68.
43. Yitshak-Sade M, James P, Kloog I, Hart JE, Schwartz JD, Laden F, Lane KJ, Fabian MP, Fong KC, Zanobetti A. Neighborhood greenness attenuates the adverse effect of PM<sub>2.5</sub> on cardiovascular mortality in neighborhoods of lower socioeconomic status. *Int J Environ Res Public Health* 2019;**16**:814.
44. Mitchell R, Popham F. Effect of exposure to natural environment on health inequalities: an observational population study. *Lancet* 2008;**372**:1655–1660.
45. Giles-Corti B, Vernez-Moudon A, Reis R, Turrell G, Dannenberg AL, Badland H, Foster S, Lowe M, Sallis JF, Stevenson M, Owen N. City planning and population health: a global challenge. *Lancet* 2016;**388**:2912–2924.
46. Münzel T, Steven S, Frenis K, Lelieveld J, Hahad O, Daiber A. Environmental factors such as Noise and Air Pollution and Vascular Disease. *Antioxid Redox Signal* 2020;**33**:581–601.
47. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binnin S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.